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Brentuximab Vedotin

Abstract

Brentuximab vedotin (cAC10-vcMMAE; SGN 35; SGN-35) is an anticancer antibody-drug conjugate under development by Seattle Genetics Inc. and its licensee Millennium: The Takeda Oncology Company. It comprises the anti-CD30 monoclonal antibody cAC10 conjugated to the cytotoxic agent monomethyl auristatin E, a synthetic analog of the tubulin polymerization inhibitor dolastatin 10. It is under investigation for use in Hodgkin lymphoma and non-Hodgkin lymphoma (specifically anaplastic large cell lymphoma) in North America and Europe. This review discusses the key development milestones and therapeutic trials of this drug.

1. Introduction

Brentuximab vedotin is an anticancer antibody-drug conjugate (ADC) product under development by Seattle Genetics Inc. (Bothell, WA, USA) and its licensee Millennium: The Takeda Oncology Company. The ADC comprises the anti-CD30 monoclonal antibody cAC10 conjugated to the cytotoxic agent monomethyl auristatin E (MMAE), a synthetic analog of the tubulin polymerization inhibitor dolastatin 10. The chimeric antibody is covalently coupled to MMAE through a valine-citrulline peptide linker. Brentuximab vedotin is designed to be stable in the bloodstream, but to release MMAE upon internalization into CD30-expressing tumor cells, resulting in a targeted cell-killing effect. The CD30 antigen is highly expressed by a variety of hematologic malignancies, including Hodgkin lymphoma and some T-cell non-Hodgkin lymphomas. Clinical development for the treatment of Hodgkin lymphoma and non-Hodgkin lymphoma (specifically anaplastic large cell lymphoma [ALCL]) is being conducted in North America and Europe.

1.1 Company Agreements

In December 2009, Seattle Genetics Inc. and Millennium: The Takeda Oncology Company, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, entered into a collaboration agreement to globally develop and commercialize brentuximab vedotin. Under the collaboration, Seattle Genetics Inc. will receive an upfront payment of $US60 million and retains full commercialization rights for brentuximab vedotin in the US and Canada. The Takeda Group will have exclusive rights to commercialize the product candidate in all countries other than the US and Canada. Seattle Genetics Inc. is entitled to receive progress and sales-dependent milestone payments in addition to tiered double-digit royalties based on net sales of brentuximab vedotin within the Takeda Group's licensed

territories. Milestone payments to Seattle Genetics Inc. could total more than $US230 million. Seattle Genetics Inc. and the Takeda Group will jointly fund worldwide development costs on a 50 : 50 basis. Development funding by the Takeda Group over the first 3 years of the collaboration is expected to be at least $US75 million. In Japan, the Takeda Group will be solely responsible for development costs.[1]

An agreement between Seattle Genetics Inc. and Albany Molecular Research for the current good manufacturing practice (cGMP) of its proprietary drug-linker system was established in May 2005. The arrangement also secures rights for ADC licensees of Seattle Genetics Inc. to work directly with Albany Molecular Research to obtain cGMP clinical trial supplies of drug-linker units.[2,3]

1.2 Key Development Milestones

Seattle Genetics Inc. plans to submit a biologics license application (BLA) to the US FDA in the first quarter of 2011. The BLA will aim to seek approval for both relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic ALCL. In Europe, Millennium: The Takeda Oncology Company has initiated discussions with regulators to support the submission of a marketing authorization application (MAA) to the European Medicines Agency (EMA) in the first half of 2011.[4]

The US FDA and the EMA have granted orphan drug designation to brentuximab vedotin for the treatment of Hodgkin lymphoma and ALCL (a type of non-Hodgkin lymphoma).[5,6] In March 2009, the FDA granted fast-track designation to brentuximab vedotin for the treatment of Hodgkin lymphoma.[7]

1.2.1 Hodgkin Lymphoma

Seattle Genetics Inc. and Millennium: The Takeda Oncology Company have initiated a phase III trial (AETHERA; NCT01100502) of brentuximab vedotin in patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant (ASCT). This randomized, double-blind, placebo-controlled trial is evaluating the safety and efficacy of brentuximab vedotin plus best supportive care (BSC) compared with placebo plus BSC. Approximately 322 patients are being enrolled at sites in the US and Europe. The primary outcome measure of the trial is progression-free survival (PFS), and secondary outcomes measures include overall survival, safety, and tolerability. Patients will receive brentuximab vedotin every 3 weeks for up to approximately 1 year. For the purposes of the trial, high-risk patients are defined as those with a history of refractory Hodgkin lymphoma, those who relapse or progress within 1 year of receiving first-line chemotherapy, and/or those who have disease outside of the lymph nodes at the time of pre-ASCT relapse.[8] Interim results were presented in December 2010. Seattle Genetics Inc. plans to submit a BLA in the first quarter of 2011 for approval of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma and systemic ALCL. Millennium: The Takeda Oncology Company plans to submit an MAA in the first half of 2011. Additionally, a limited patient access program for qualified patients will be set up in the US in early 2011. Outside of the US and Canada, brentuximab vedotin will be available to qualified patients through a Named Patient Programme.[9]

Seattle Genetics Inc. and Millennium: The Takeda Oncology Company initiated a phase II/III study (NCT01196208) of brentuximab vedotin in patients with Hodgkin lymphoma who received placebo in the phase III AETHERA trial (SGN35-0005). The trial expects to enroll up to 80 patients by invitation only and aims to be completed by December 2011.

In February 2009, Seattle Genetics Inc. initiated a single-arm pivotal phase II trial (NCT 00848926) to assess the efficacy and safety of single-agent brentuximab vedotin (1.8 mg/kg every 3 weeks) in 102 patients with relapsed or refractory Hodgkin lymphoma under a special protocol assessment agreement. The primary endpoint of the study will be objective response rate and secondary endpoints to include duration of response, PFS, overall survival, and tolerability. The company completed enrollment of patients at more than 30 sites in the US, Canada, and Europe in August 2009. Top-line data were

reported by Seattle Genetics Inc. and Millennium: The Takeda Oncology Company in September 2010.[10]

In July 2009, Seattle Genetics Inc. initiated a multicenter, phase II trial (NCT00947856) investigating the efficacy and tolerability of retreatment with brentuximab vedotin (1.8 mg/kg every 3 weeks) in patients with relapsed or refractory Hodgkin lymphoma or systemic ALCL who had previously responded to brentuximab vedotin. The trial is expected to enroll 125 patients and is taking place in the US and Europe.[11,12]

In January 2010, Seattle Genetics Inc. and Millennium: The Takeda Oncology Company initiated an open-label, single-arm phase I trial (SGN35-009; NCT01060904) of brentuximab vedotin in combination with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) in the treatment of patients with newly diagnosed Hodgkin's lymphoma. The dose-escalation trial will enroll 40 patients in the US and Canada.[13]

1.2.2 Non-Hodgkin Lymphoma (including Anaplastic Large Cell Lymphoma)

In June 2009, Seattle Genetics Inc. initiated a pivotal phase II study (NCT00866047) of single-agent brentuximab vedotin (1.8 mg/kg every 3 weeks) in patients with relapsed or refractory systemic ALCL. Recruitment of 58 patients from centers in the US, Canada, and the EU was completed in May 2010. Preliminary, top-line results have been reported.[14-17]

In July 2009, Seattle Genetics Inc. initiated a multicenter, phase II trial (NCT00947856) investigating the efficacy and tolerability of retreatment with brentuximab vedotin (1.8 mg/kg every 3 weeks) in patients with systemic ALCL or relapsed or refractory Hodgkin lymphoma who had previously responded to brentuximab vedotin. The trial is expected to enroll 125 patients and is taking place in the US and Europe.[11,12]

1.2.3 General Hematologic Malignancies

Seattle Genetics Inc. has conducted a phase I trial (NCT00430846) of brentuximab vedotin (given every 21 days) in 44 refractory patients with Hodgkin lymphoma or CD30-positive hematologic malignancies. The trial evaluated the safety and pharmacokinetics of brentuximab vedotin among patients enrolled at multiple centers throughout the US. Data presented in December 2008 demonstrated multiple complete and partial responses at well tolerated doses.[18-20]

Seattle Genetics Inc. and Millennium: The Takeda Oncology Company are also conducting a phase I study to assess the cardiac safety of brentuximab vedotin in patients with CD30-positive hematologic cancers (NCT01026233).[21] The study was expected to be completed in August 2010 but as of February 2011, the companies have completed enrollment of 40 patients and the trial is ongoing.

A phase I trial (NCT00649584) was initiated in the US in March 2008, to evaluate brentuximab vedotin in 72 patients with refractory or relapsed CD30-positive hematologic malignancies (Hodgkin lymphoma or systemic ALCL). The study was expected to be completed in December 2010. However, this trial was terminated as Seattle Genetics Inc. decided not to enroll cohorts of combined brentuximab vedotin and gemcitabine therapy.[17,22-24]

1.3 Patent Information

The US Patent and Trademark Office has issued Seattle Genetics Inc. with a patent related to its ADC technology. US Patent No. 7 659 241, covers cleavable linkers and potent auristatin drug payloads used in certain Seattle Genetics Inc. ADC programs, including brentuximab vedotin.[25]

Seattle Genetics Inc. was issued a US patent covering the cell-killing component of brentuximab vedotin in May 2005.[3]

2. Scientific Summary

2.1 Pharmacokinetics

***Phase I*:** Area under the concentration-time curve (AUC) increased relative to dose level of brentuximab vedotin in this phase I trial. The trial enrolled patients with relapsed or refractory CD30-positive lymphomas (n = 37) and brentuximab vedotin was administered weekly for 3 weeks in 28-day treatment cycles at doses of 0.4–1.4 mg/kg (30 minute or 2 hour intravenous infusions).[26]

Table I. Features and properties

Alternate names	cAC10-vcMMAE; SGN 35; SGN-35
Originator	Seattle Genetics Inc.
Licensee(s)	Millennium: The Takeda Oncology Company
Highest development phase	III (Europe, US)
Active development indications	Hodgkin lymphoma, Non-Hodgkin lymphoma
Class	Auristatins, drug conjugates, monoclonal antibodies
Mechanism of action	Tubulin polymerization inhibitors
CAS Registry number	914088-09-8
Route of administration	IV
Pharmacodynamics	Potent cytotoxic activity against CD30-expressing cells *in vitro*; associated with disease-free survival mouse Hodgkin lymphoma model; dose-dependent antitumor activity in preclinical models of anaplastic large cell lymphoma; has superior antitumor efficacy compared with non-targeted drugs, in preclinical models of Hodgkin lymphoma
ATC codes	
WHO ATC code	L01 (Antineoplastic Agents), L01X-C (Monoclonal antibodies)
EphMRA ATC code	L1 (Antineoplastics), L1X3 (Antineoplastic monoclonal antibodies)
Adverse events	
Occasional	Alopecia, diarrhea, fatigue, fever, injection-site reactions, musculoskeletal pain, nausea, neutropenia, peripheral nervous system diseases, thrombocytopenia

AUC increased relative to dosage and did not accumulate with repeated dosing in a phase I dose-escalation trial in patients with hematologic malignancies.[27]

***Preclinical*:** The elimination half-life of brentuximab vedotin in mice was approximately 5 days and the maximum tolerated dose was >30 mg/kg.[28]

2.2 Adverse Events

***Phase III*:** In the interim results from the ATHERA trial of brentuximab vedotin in patients at high risk of residual Hodgkin lymphoma following ASCT, the most common adverse events were peripheral sensory neuropathy (47%), fatigue (46%), nausea (42%), upper respiratory tract infection (37%), and diarrhea (36%). The most common grade 3 or 4 adverse events were neutropenia (20%), peripheral sensory neuropathy (8%), thrombocytopenia (8%), and anemia (6%).[9]

***Phase II*:** Brentuximab vedotin demonstrated a similar safety and tolerability profile to prior clinical studies in a phase II trial of 102 patients with relapsed or refractory Hodgkin lymphoma. In this open-label trial, patients received brentuximab vedotin (1.8 mg/kg) every 3 weeks for a maximum of 16 doses.[10]

Brentuximab vedotin was associated with manageable adverse events in a phase II clinical trial in 58 patients with relapsed or refractory systemic ALCL. The most common adverse events were nausea (38%), peripheral neuropathy (38%), fatigue (34%), fever (33%), and diarrhea (29%). The most common grade 3 or higher adverse events were neutropenia (21%), peripheral neuropathy (10%), thrombocytopenia (14%), and anemia (7%).[4]

***Phase I*:** In a phase I trial, brentuximab vedotin exceeded a maximum tolerated dose at 1.4 mg/kg and exhibited grade 3 dose-limiting toxicities of diarrhea and vomiting, and hyperglycemia grade 4. The most common drug-associated adverse events were peripheral neuropathy, nausea, fatigue, diarrhea, dizziness, and neutropenia; most were grade 1 or 2 in severity. The trial enrolled patients with relapsed or refractory CD30-positive lymphomas (n = 37) and brentuximab vedotin was administered weekly for 3 weeks in 28-day treatment cycles at doses of 0.4–1.4 mg/kg (30 minute or 2 hour intravenous infusions).[26]

Brentuximab vedotin was generally well tolerated in a phase I trial among 44 evaluable

Table II. History

Event Date	Update type	Comment	Update date
7 December 2010	Scientific Update	Efficacy and adverse events data from a phase II trial in anaplastic large cell lymphoma presented at the 52nd Annual Meeting and Exposition of the American Society of Hematology (ASH-2010)[4]	11 December 2010
6 December 2010	Scientific Update	Interim efficacy and adverse events data from the phase III AETHERA trial in Hodgkin lymphoma presented at the 52nd Annual Meeting and Exposition of the American Society of Hematology (ASH-2010)[9]	9 December 2010
5 December 2010	Scientific Update	Additional efficacy data from a phase II trial in Hodgkin lymphoma presented at the 52nd Annual Meeting and Exposition of the American Society of Hematology (ASH-2010)[37]	7 December 2010
11 October 2010	Scientific Update	Efficacy data from a phase II trial (NCT00866047) in relapsed and refractory non-Hodgkin lymphoma (anaplastic large cell lymphoma) released by Seattle Genetics Inc. and Millennium: The Takeda Oncology Company[14]	12 October 2010
27 September 2010	Scientific Update	Efficacy data from a pivotal phase II trial in relapsed and refractory Hodgkin lymphoma released by Seattle Genetics Inc. and Millennium: The Takeda Oncology Company[10]	1 October 2010
8 June 2010	Scientific Update	Interim efficacy and adverse events data from a clinical trial in Hodgkin lymphoma and systemic anaplastic large cell lymphoma (non-Hodgkin lymphoma) presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[31]	15 June 2010
24 May 2010	Trial Update	Seattle Genetics Inc. completes enrollment in its phase II trial for relapsed/refractory anaplastic large cell lymphoma in the US, EU, and Canada	26 May 2010
30 April 2010	Trial Update	Seattle Genetics Inc. terminates the phase I trial of brentuximab alone and in combination with gemcitabine for CD30-positive hematologic malignancies	19 May 2010
10 April 2010	InThought Forecasts	inThought Analysis for Hodgkin lymphoma updated	10 April 2010
30 March 2010	Phase Change	Phase III clinical trials in Hodgkin lymphoma (patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant) in Europe (IV)	15 February 2011
30 March 2010	Phase Change	Phase III clinical trials in Hodgkin lymphoma (patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant) in the US (IV)	30 March 2010
29 January 2010	Phase Change	Phase I clinical trials (combination therapy) in Hodgkin lymphoma in Canada (IV)	5 February 2010
29 January 2010	Phase Change	Phase I clinical trials (combination therapy) in Hodgkin lymphoma in the US (IV)	5 February 2010
16 December 2009	Licensing Status	Seattle Genetics Inc. enters into a licensing agreement with Millennium: The Takeda Oncology Company[1]	17 December 2009
8 December 2009	Scientific Update	Efficacy, pharmacokinetic, and adverse events data from a phase I trial in Hodgkin lymphoma and non-Hodgkin lymphoma presented at the 51st Annual Meeting and Exposition of the American Society of Hematology (ASH-2009)[26]	9 December 2009
5 December 2009	Scientific Update	Updated interim efficacy and adverse events data from a phase I trial in Hodgkin lymphoma and CD30-positive lymphoma presented at the 51st Annual Meeting and Exposition of the American Society of Hematology (ASH-2009)	31 December 2009

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Table II. Contd

Event Date	Update type	Comment	Update date
8 September 2009	Scientific Update	Further updated efficacy data from a phase I trial in Hodgkin lymphoma and CD30-positive hematologic malignancies released by Seattle Genetics Inc.[29]	16 September 2009
25 August 2009	Trial Update	Seattle Genetics Inc. completes enrollment in its phase II trial for brentuximab vedotin in Hodgkin lymphoma in the US, Canada, and Europe	31 August 2009
25 July 2009	Trial Update	Seattle Genetics Inc. initiates a phase II trial of retreatment in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma in the US[11]	28 July 2009
23 July 2009	Scientific Update	Pharmacodynamics data from a preclinical trial in Hodgkin lymphoma presented at the 100th Annual Meeting of the American Association for Cancer Research (AACR-2009)[36]	23 July 2009
19 June 2009	Phase Change	Phase II clinical trials in non-Hodgkin lymphoma in Canada (IV)	23 June 2009
2 June 2009	Scientific Update	Interim efficacy and adverse events data from a phase I trial in hematologic malignancies presented at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO-2009)[23]	8 June 2009
31 March 2009	Regulatory Status	Brentuximab vedotin receives fast-track designation for Hodgkin lymphoma (IV, infusion) in the US	1 April 2009
19 March 2009	Phase Change	Phase II clinical trials in non-Hodgkin lymphoma in the EU (IV)	19 June 2009
19 March 2009	Phase Change	Phase II clinical trials in non-Hodgkin lymphoma in the US (IV)	19 June 2009
20 February 2009	Phase Change	Phase II clinical trials in Hodgkin lymphoma in Canada (IV)	23 February 2009
20 February 2009	Phase Change	Phase II clinical trials in Hodgkin lymphoma in Europe (IV)	23 February 2009
20 February 2009	Phase Change	Phase II clinical trials in Hodgkin lymphoma in the US (IV)	23 February 2009
20 February 2009	Trial Update	Seattle Genetics Inc. initiates enrollment in a phase II trial for Hodgkin lymphoma in Canada, Europe, and the US	23 February 2009
27 January 2009	Regulatory Status	Brentuximab vedotin receives orphan drug status for non-Hodgkin lymphoma in the EU	28 January 2009
27 January 2009	Regulatory Status	Brentuximab vedotin receives orphan drug status for Hodgkin lymphoma in the EU	28 January 2009
27 January 2009	Regulatory Status	Brentuximab vedotin receives orphan drug status for non-Hodgkin's lymphoma in the US	28 January 2009
8 December 2008	Scientific Update	Updated efficacy data from a phase I trial in hematologic malignancies presented at the 50th Annual Meeting and Exposition of the American Society of Hematology (ASH-2008)[18]	10 December 2008
25 October 2008	Scientific Update	Interim efficacy data from a phase I trial in hematologic malignancies presented at the 20th-EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)[19]	28 October 2008
24 October 2008	Scientific Update	Pharmacodynamic data from a preclinical trial in hematologic malignancies presented at the 20th-EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)[35]	12 November 2008
4 June 2008	Scientific Update	Interim efficacy and adverse events data from a phase I trial in Hodgkin lymphoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[30]	11 June 2008
3 June 2008	Scientific Update	Pharmacokinetics data from a phase I trial in Hodgkin lymphoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[27]	18 June 2008

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Table II. Contd

Event Date	Update type	Comment	Update date
31 March 2008	Trial Update	Seattle Genetics Inc. initiates enrollment in a second phase I trial for refractory or relapsed CD30-positive hematologic malignancies in the US	2 April 2008
8 November 2007	Scientific Update	Interim results from a phase I clinical trial in patients with hematologic malignancies added to the adverse events and cancer therapeutic trials sections[20]	8 November 2007
15 February 2007	Regulatory Status	Brentuximab vedotin receives orphan drug status for Hodgkin lymphoma in the US	15 February 2007
22 November 2006	Phase Change	Phase I clinical trials in hematologic malignancies in US (IV)	22 November 2006
8 August 2006	Regulatory Status	Seattle Genetic Inc. has filed an IND with the US FDA for the treatment of Hodgkin lymphoma and other CD-positive hematologic malignancies	8 August 2006
13 September 2005	Scientific Update	Data presented at the 9th International Conference on Malignant Lymphoma (ICML-2005) have been added to the cancer pharmacodynamics section[34]	13 September 2005
15 June 2005	Scientific Update	Preclinical data from a media release have been added to the cancer pharmacodynamics section[33]	15 June 2005
15 July 2004	Licensing Status	Seattle Genetics Inc. enters preferred provider agreement with Albany Molecular Research for antibody-drug conjugate manufacturing[2]	15 July 2004
12 September 2003	Scientific Update	A preclinical study has been added to the adverse events section[32]	12 September 2003
22 July 2003	Scientific Update	Data presented at the 94th Annual Meeting of the American Association for Cancer Research (AACR-20-03) have been added to the cancer pharmacodynamics and pharmacokinetics section[28]	22 July 2003
28 May 2003	Phase Change	Preclinical trials in hematologic malignancies in the US (IV)	28 May 2003

patients with Hodgkin lymphoma and CD30-positive hematologic malignancies. The majority of adverse events were grade 1 and 2, with the most common being fatigue, fever, diarrhea, nausea, and peripheral neuropathy. The maximum tolerated dose was defined as 1.8 mg/kg. Patients received doses of brentuximab vedotin every 3 weeks, escalating from 0.1 mg/kg to 3.6 mg/kg. Dose-limiting toxicities of hyperglycemia, prostatitis, and neutropenic fever were observed at 2.7 mg/kg. One patient treated at 3.6 mg/kg experienced fever, neutropenia, and sepsis, and died 14 days after the first dose of brentuximab vedotin. An additional two patients developed a positive anti-therapeutic antibody response to brentuximab vedotin in preliminary analyses. Less than 10% of brentuximab vedotin doses were delayed due to toxicity, primarily neutropenia, at higher doses.[18,20,29,30]

In an open-label, uncontrolled, phase I trial evaluating weekly dosing for refractory or relapsed lymphoma (Hodgkin or systemic ALCL), interim results for 35 evaluable patients showed that brentuximab vedotin was generally well tolerated. The majority of adverse events were grade 1 and 2, with the most common being fatigue, nausea, neutropenia, and peripheral neuropathy. Patients received weekly doses of 0.4–1.4 mg/kg, for 3 of 4 weeks, for a minimum of two cycles.[22,23]

Preliminary data from 11 patients with Hodgkin lymphoma (n = 9) and systemic ALCL (non-Hodgkin lymphoma; n = 2) who received retreatment with brentuximab vedotin monotherapy have shown that the drug was well tolerated in this setting. All drug-related adverse events were grade 1 or 2, with the most common events being peripheral neuropathy, hair loss (alopecia), joint pain (musculoskeletal pain), and injection-site irritation. Patients were heavily pretreated with a range of 2–11 prior therapies. Five patients had received a prior ASCT. Patients had achieved

Table III. Forecasts

InThought Probability of Approval[a]			
Indication	Approval Date Estimate	inThought Approvability Index	Last Update
Hodgkin lymphoma	NE	63% (NYR)	10 Apr 2010
Non-Hodgkin lymphoma	NE	31% (NYR)	30 Jul 2009

a The Wolters Kluwer Health Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with 'A' indicating significantly above average/likely to progress, 'C' indicating average, and 'F' indicating significantly below average/unlikely to progress. 'NYR' stands for 'Not Yet Rated,' indicating that the probability of approval is based on historical approval rates for similar drugs according to indication, molecule type, novelty, and phase, but without analyses of clinical data, trial design, and other factors specific to the individual agent.

NE = no estimate.

stable disease with decreasing tumor volume or better during prior treatment with brentuximab vedotin, discontinued treatment, and subsequently experienced disease progression.[31]

***Animal Toxicology*:** In severe combined immunodeficiency (SCID) mouse xenograft models of ALCL or Hodgkin lymphoma, mice treated with brentuximab vedotin 30 mg/kg showed no signs of toxicity.[32]

2.3 Pharmacodynamics

2.3.1 Cancer

***Preclinical*:** *In vitro* studies showed that the peptide linkage in brentuximab vedotin was efficiently cleaved by lyosomal proteases following CD30 binding and internalization, releasing the fully active drug compound, MMAE into the cell cytosols. This resulted in growth arrest in G2/M phase, apoptosis, and death. Brentuximab vedotin had potent cytotoxic activity against CD30-expressing cells (50% inhibitory concentration [IC_{50}] <10 ng/mL) but was 300-fold less potent against antigen-negative cells. *In vivo* studies showed that 80% of Hodgkin lymphoma and ALCL xenografted mice treated with brentuximab vedotin survived disease-free at doses as low as 1 mg/kg.[28,32]

In preclinical models of ALCL, brentuximab vedotin displayed IC_{50} values ranging from 3.9 to 15.8 ng/mL against CD30+ cell lines, and an IC_{50} >1000 ng/mL against the CD30 line WSU-NHL. In a SCID mouse model of ALCL, brentuximab vedotin exhibited dose-dependent antitumor activity, with complete regressions achieved using doses ≥0.5 mg/kg (with repeat dosing) and ≥1 mg/kg (with single dosing).[33,34]

Preclinical studies in animal models of Hodgkin lymphoma indicated that brentuximab vedotin localized in tumor tissue and had potent antitumor activity whether administered alone or in combination with chemotherapy. When combined with doxorubicin, bleomycin, vinblastine, and dacarbazine, or gemcitabine, the antitumor activity was markedly better than with brentuximab vedotin alone or chemotherapy alone. Combination therapy was not associated with alterations in CD30 expression in tumors.[35]

Preclinical data have demonstrated the superior antitumor activity of brentuximab vedotin in Hodgkin lymphoma, compared with that of several non-targeted drugs, including vinorelbine, vinblastine, and unconjugated MMAE. Due to the targeting ability of brentuximab vedotin, concentrations of MMAE within tumors were up to 30-fold higher than the non-targeted drugs. Also, MMAE concentrations in tumors were 1000-fold greater than MMAE blood concentrations following brentuximab vedotin administration.[36]

2.4 Therapeutic Trials

2.4.1 Cancer

***Phase III*:** In interim results from the ATHERA trial of brentuximab vedotin in patients at high risk of residual Hodgkin lymphoma following ASCT, 75% of patients achieved an objective response, including 34% complete remissions,

and 40% partial remissions. The median duration of response was 29 weeks by independent central review and 47 weeks by investigator assessment. Stable disease was observed in 22% of patients, of which 3% had progressive disease and one patient was not evaluable for response. Tumor reductions were achieved in 94% of patients. PFS among all patients was 25 weeks by independent review and 39 weeks by investigator assessment. PFS among patients achieving a complete remission and median overall survival had not yet been reached at a median follow-up of approximately 1 year.[9]

***Phase II*:** Treatment with brentuximab vedotin caused tumor reductions in 94% of patients with relapsed or refractory Hodgkin lymphoma in a pivotal, open-label phase II trial (n = 102). Furthermore, 75% of patients had an objective response that lasted for ≥6 months. Brentuximab vedotin (1.8 mg/kg) was administered every 3 weeks for up to a total of 16 doses.[10,14,37]

Results from a phase II single-arm clinical trial with brentuximab vedotin (1.8 mg/kg every 3 weeks for up to 16 total doses) in 58 patients with relapsed or refractory systemic ALCL showed an objective response in 86% of patients. Complete remission was achieved in 53% of patients. The rate of partial remissions was 33%, 3% of patients had stable disease, and 5% had progressive disease.[4]

***Phase I*:** In a phase I study, brentuximab vedotin lead to an objective response rate in evaluable patients of 46%, with 29% achieving complete remission. Median duration of response to date was at least 16 weeks with 15 patients continuing treatment. The trial enrolled patients with relapsed or refractory CD30+ lymphomas (n = 37) and brentuximab vedotin was administered weekly for 3 weeks in 28-day treatment cycles at doses of 0.4–1.4 mg/kg (30 minute or 2 hour intravenous infusions).[26]

In a phase I trial of brentuximab vedotin among 44 evaluable patients with Hodgkin lymphoma and CD30+ hematologic malignancies, 17 patients achieved objective responses, including nine complete responses and eight partial responses. A total of 18 additional patients had stable disease and nine patients progressed. The median duration of response was 22 weeks, with 11 responses ongoing at the time results were published. Across all dose levels, 86% of the 42 patients who had at least one post-baseline assessment achieved reductions in tumor volume. Among 28 evaluable patients treated at doses of 1.2 mg/kg and higher, 54% achieved an objective response, including 32% with complete responses. Additionally, 93% of these patients achieved tumor reductions, and their mean PFS was greater than 6 months. Patients received doses of brentuximab vedotin every 3 weeks, escalating from 0.1 mg/kg to 3.6 mg/kg.[18,19,20,30] A further update showed that the objective response rate (combining all dose levels) was 39% (based on investigator assessment) and 41% (based on independent review). In patients who received brentuximab vedotin at doses of ≥1.2 mg/kg, the overall response rate was 54% (based on investigator assessment) and 57% (based on independent review). The median duration of response was ≥7.3 months and eight patients remained in ongoing response.[29]

In an open-label, uncontrolled, phase I trial evaluating weekly brentuximab vedotin dosing for refractory or relapsed CD30+ lymphoma (Hodgkin or systemic ALCL), interim results showed that 16 of 35 evaluable patients achieved objective responses (ten complete responses). Eleven patients had stable disease and three had progressive disease. The median duration of response is ≥16 weeks, with 15 patients still receiving treatment. Patients received weekly doses of 0.4–1.4 mg/kg, for 3 of 4 weeks, for a minimum of two cycles.[22,23]

Preliminary data from 11 patients with Hodgkin lymphoma (n = 9) and systemic ALCL (non-Hodgkin lymphoma; n = 2) who were retreated with brentuximab vedotin monotherapy have shown that objective responses were achieved in seven retreated patients (64% of patients, including two complete remissions and five partial remissions). Tumor reductions were observed in 10 of 11 retreated patients. All patients were heavily pretreated (i.e. 2–11 prior therapies). Five patients had received a prior ASCT. Patients had achieved stable disease with decreasing tumor volume or better during prior treatment with brentuximab vedotin, discontinued treatment,

and subsequently experienced disease progression. The time to objective response ranged from 5 to 15 weeks. Three patients showed stable disease and one had progressive disease. The duration of retreatment objective responses ranged from <1 week (retreatment ongoing), to >58 weeks. Based on the small sample size, no difference in duration of retreatment response between patients with Hodgkin lymphoma and non-Hodgkin lymphoma (ALCL) was observed. Retreatment is ongoing in three patients.[31]

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